MAY 2 6 2011

FUJIREBIO® Diagnostics, Inc.

510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K100831.

Submitter Information

Address: Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355

Contact person: Diana Dickson
(610) 240-3917
dicksond@fdi.com

Summary preparation date: May 26, 2011

Name of Device

Trade/Proprietary Name: CYFRA 21-1 EIA Kit

Common/Usual Name: CYFRA 21-1 EIA Test Kit

Regulation Number: 21 CFR 866.6010

Regulatory Class: Class II

Product Code: OVK

Predicate Device

ARCHITECT CEA (K990774)

Device Description

The CYFRA 21-1 EIA is a solid phase, non-competitive immunoassay based on two monoclonal antibodies (derived from mice) directed against two separate antigenic determinants of soluble fragments of cytokeratin 19. Calibrators, controls and patient samples are incubated together with biotinylated Anti-CYFRA 21-1 MAb and horseradish peroxidase (HRP) labeled Anti-CYFRA 21-1 MAb in streptavidin coated micro strips. After washing, buffered Substrate/Chromogen reagent (hydrogen peroxide and 3, 3', 5, 5' tetramethylbenzidine) is added to each well and the enzyme reaction is allowed to proceed. During the enzyme reaction a blue color will develop if antigen is present. The intensity of the color development is proportional to the amount of CYFRA 21-1 present in the samples.

The color intensity is determined in a microplate spectrophotometer at 620 nm (or optionally at 405 nm after addition of Stop Solution).

Calibration curves are constructed for each assay by plotting absorbance value versus the concentration for each calibrator. The CYFRA 21-1 concentrations of patient samples are then read from the calibration curve.

Reportable Range

The CYFRA 21-1 EIA measures concentrations between 0.5 and 50 ng/mL.

Intended Use

The CYFRA 21-1 EIA kit is intended for the quantitative determination of soluble cytokeratin 19 fragments in human serum. The assay is to be used as an aid in monitoring disease progression during the course of disease and treatment in lung cancer patients. Serial testing for patient CYFRA 21-1 assay values should be used in conjunction with other clinical methods used for monitoring lung cancer.

Statement of Substantial Equivalence

The CYFRA 21-1 EIA kit is intended for the quantitative determination of soluble cytokeratin 19 fragments in human serum.
The assay is to be used as an aid in monitoring disease progression during the course of disease and treatment in lung cancer patients. Serial testing for patient CYFRA 21-1 assay values should be used in conjunction with other clinical methods used for monitoring lung cancer.

As there is no FDA cleared or approved device for the CYFRA 21-1 EIA Kit, substantial equivalence for the CYFRA 21-1 EIA test kit was determined by comparing the performance characteristics obtained with the CYFRA 21-1 EIA to the package insert claims in the ARCHITECT CEA assay.

The regulatory submission will be prepared pursuant to Title 21CFR § 866.6010(b) which states Tumor Markers must comply with the following special controls;

1. Guidance document entitled "Guidance Document for the Submission of Tumor Associated Antigen Premarket Notifications (510(k)s) to FDA".

2. Voluntary assay performance standards issued by the Clinical Laboratory Standards Institute (CLSI), formally NCCLS.

A comparison of the features of the CYFRA 21-1 EIA Kit and the ARCHITECT CEA assay are as follows:

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Similarities		
	CYFRA 21-1 EIA Kit (Proposed Device)	**ARCHITECT CEA (Predicate Device) K990774**
Device Type	*In vitro* diagnostic	*In vitro* diagnostic
Classification	Class II	Class II
Regulation Number	21 CFR 866.6010	21 CFR 866.6010
Product Usage	Clinical and Hospital laboratories	Clinical and Hospital laboratories
Specimen Collection Method	Routine Phlebotomy Techniques	Routine Phlebotomy Techniques
Interpretation of Results	Standard Curve	Standard Curve

Differences		
	CYFRA 21-1 EIA Kit (Proposed Device)	**ARCHITECT CEA (Predicate Device) K042731**
Product Code	To be determined	DHX
Type of Specimen	Human Serum Only	Human Serum or Plasma
Antigen Detected	CYFRA 21-1	CEA
Calibrators	Supplied with Kit	Supplied as separate Kit
Controls	Supplied with Kit	Supplied as separate Kit
Principle of Operation	Manual Enzymatic Immunoassay (EIA)	Automated Chemiluminscent Microparticle Immunoassay (CMIA)
Intended Use	Aid in monitoring disease progression during the course of disease and treatment in lung cancer patients.	Aid in the prognosis and management of cancer patients in whom changing concentrations of CEA are observed.

Performance Characteristics

Precision:

Two (2) sites tested two (2) CYFRA 21-1 EIA Kit lots for the precision study. For each lot, the two (2) sites repeated the assay for twenty (20) days, (twenty (20) days each lot), and performed two (2) runs per day with four (4) serum based panel samples tested as unknowns. One (1) site tested three (3) CYFRA 21-1 EIA Kit lots for the precision study. This site repeated the assay for thirty (30) days (ten (10) days each lot), performing two (2) runs per day with eight (8) serum based panel samples tested as unknowns. The total precision of the CYFRA 21-1 EIA was found to be < 8.6 %.

Linearity:

The CYFRA 21-1 EIA assay mean dilution linearity is 100 ± 20%. A study was conducted for the CYFRA 21-1 EIA Kit modeled after the CLSI guideline EP6-A. Serum samples with elevated CYFRA 21-1 values were diluted with CYFRA 21-1 Calibrator A (zero). The CYFRA 21-1 concentration was determined for each dilution and the percent (%) recovery was calculated. The nonlinearity calculated by weighted polynomial regression is ≤ 10% across the measurement range of 0.5 to 50.0 ng/mL.

Detection and Quantitation Limit:

The Limit of Detection of the CYFRA 21-1 EIA Kit was determined to be 0.12 ng/mL. The CLSI guideline EP17-A (22) was used to design the LoD experiments. The limit of detection (LoD) corresponds to the upper limit of the 95% confidence interval and represents the lowest concentration of CYFRA 21-1 antigen that can be distinguished from zero.

The Limit of Quantitation of the CYFRA 21-1 EIA Kit was determined to be 0.21 ng/mL. The limit of quantitation (LoQ) corresponds to the lowest amount of analyte in a sample that can be accurately quantitated with the highest allowable imprecision of 17.78%.

Interference:

The CYFRA 21-1 EIA Kit mean assay specificity is 100 ± 15%. Recovery studies were performed to compare sera containing the following compounds at the indicated concentrations with control sera. The CLSI guideline EP7-A was used to design the interference experiments. The following substances and concentrations were tested and found not to interfere with the test.

Endogenous serum interferences	Test Concentration
Triglycerides	30 mg/mL
Billirubin	0.2 mg/mL
Hemoglobin	5 mg/mL
Total Protein	120 mg/mL
Chemotherapeutic drug interferences	**Test Concentration**
Carboplatin	500 µg/mL
Cisplatin	165 µg/mL
Dexamethasone	10 µg/mL
Doxorubicin	1.16 µg/mL
Leucovorin	2.68 µg/mL
Methotrexate	45 µg/mL
Paclitaxel	3.5 ng/mL

Potentially interfering clinical conditions

The CYFRA 21-1 EIA assay was evaluated using specimens with HAMA and Rheumatoid Factor (RF) to further assess the assay specificity. Six specimens positive for HAMA and five specimens positive for RF were evaluated for % recovery with CYFRA 21-1 antigen spiked into each specimen at approximately 5 and 25 ng/mL.

Clinical condition	Number of specimens	Mean % recovery
HAMA	6	98
RF	5	101

MONITORING THE COURSE OF DISEASE IN PATIENTS DIAGNOSED WITH LUNG CANCER

The effectiveness of the CYFRA 21-1 EIA as an aid in monitoring the course of disease in lung cancer patients was determined through a retrospective clinical study. Changes in CYFRA 21-1 levels in serial serum samples collected from a tertiary cancer center were compared to changes in disease status. A study involving 100 patients was undertaken with a total of 314 observation pairs with an average number of 4.1 observations per patient. For the 100 lung cancer cases, 95 were classified as non-small cell lung cancer (NCSLC) and 5 were classified as small cell lung cancer (SCLC). 90 of the NSCLC were further classified as adenocarcinoma (68), squamous cell carcinoma (19), and large cell carcinoma (3). 79 of these the 100 lung cancer cases had staging information as shown in the following table. In this study, only 5 patients had Stage I or II disease, the performance of CYFRA 21-1 has not been adequately assessed in this subpopulation.

	Number of Patients
Stage I	2
Stage II	3
Stage III	36
Stage IV	38
Total (with Stage Information)	***79***
Unknown	17
Unstaged	4
Total Lung Cancer Cases	***100***

A positive change in CYFRA 21-1 was defined as a measurable increase in the value that was at least 50% greater than the previous value of the test. Observation pairs with both values below the normal reference range of 1.8 ng/mL were defined as no significant change. This level of change takes into account the variability of the assay and the biological variability.

Forty-six percent (46%) or 39/85 of the patient samples with a positive change correlated with the disease progression while eighty-seven percent (87%) or 200/229 of the patient serial samples with no significant change in CYFRA 21-1 value correlated with no progression. The total concordance was seventy-six percent (76%) or 239/314. The following table presents the data in a 2 x 2 format.

Change in Disease State per Sequential Pair			
Increase in CYFRA 21-1 concentration	**Progression**	**No Progression**	**Total**
>50%	39	29	68
≤50%	46	200	246
Total	85	229	314

Clinicians may wish to use other percent changes in CYFRA 21-1 concentration to reflect their preferences in the trade-off between sensitivity and specificity. The following table shows the resulting sensitivities and specificities of the CYFRA 21-1 EIA at various percent changes in CYFRA 21-1 EIA concentrations, together with the positive predictive values (PPV) and negative predictive values (NPV) for the population tested (85 sequential pairs from patients with disease progression and 229 sequential pairs from patients with no progression.)

- Sensitivity is represented as the proportion of patients with disease progression that had elevated CYFRA 21-1
- Specificity is represented as the proportion of patients without disease progression that had no elevation in CYFRA 21-1
- PPV is represented as the proportion of patients with elevated CYFRA 21-1 that had disease progression
- NPV is represented as the proportion of patients with no elevation in CYFRA 21-1 that did not have disease progression

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Percent Increase in CYFRA 21-1 Concentration (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
30	52.9	84.3	55.6	82.8
40	48.2	85.6	55.4	81.7
50	45.9	87.3	57.4	81.3
60	44.7	88.2	58.5	81.1
70	43.5	89.5	60.7	81.0

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

Fujirebio Diagnostics, Inc.
c/o Ms. Diana Dickson
Regulatory Affairs Manager
201 Great Valley Parkway
Malvern, PA 19355

MAY 26 2011

Re: k100831
Trade/Device Name: CYFRA 21-1 EIA Kit
Regulation Number: 21 CFR §866.6010
Regulation Name: Tumor-associated antigen immunological test system
Regulatory Class: Class II
Product Codes: OVK
Dated: May 18, 2011
Received: May 19, 2011

Dear Ms. Dickson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice

requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use Form

510(k) Number (if known): K100831

Device Name: CYFRA 21-1 EIA

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Prescription Use X (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) k100831